UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,724	02/09/2001	Sergio A. Lira	JB01066Q	6914

24265 7590 09/10/2003

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,724	LIRA, SERGIO A.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption of the endogenous CCR8 gene wherein the mouse exhibits a defective Th2 response in allergen challenged mice, does not reasonably provide enablement for the other animals encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are directed a genetically engineered non-human animal (claims 12-14) and embryo (claim 15) lacking a CCR8 gene.

The specification teaches targeted gene insertion which replaces the CCR8 gene with the neomycin resistance gene in mice (pages 21-22, Example II). Gene targeting of mouse ES cells was performed in vitro and the transformed ES cells were microinjected into mouse blastocysts (page 26, lines 9-10), resulting in chimeric mice. The mice were bred to generate a transgenic line lacking a CCR8 gene. The specification teaches that the mice lacking a CCR8 gene have no obvious phenotype in comparison to wildtype mice (page 23, lines 10); however, when challenged by infection with *Schistosoma mansoni* eggs or cockroach allergen, the mice exhibit

a defective Th2 type immune response (pages 23-25, specifically page 24, lines 21-25 and page 25, lines 3-15; pages 29-32).

The breadth of claims 12-13 and 15 encompasses non-mouse species of animals lacking a CCR8 gene. However, the specification only teaches mice lacking a CCR8 gene and fails to provide adequate guidance for making and using the other species of animals encompassed by the claims. Because claims 12-15 fail to recite a phenotype for the claimed animals, the breadth of these claims includes the claimed animals exhibiting any phenotype.

The state of the art at the time of filing held that targeted gene insertion technology was not available for any species other than mouse. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) and Lederman (2000, Experimental Physiology, Vol. 85, pages 603-613) taught that non-mouse ES cells capable of providing germline chimeras were not available (see Mullins, page S38, column 1, first paragraph). Also, Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Thus, at the time of filing, the state of the art held that gene-targeted animals could not be prepared for any species other than mouse. There is a lack of guidance in the specification to overcome the undeveloped state of the art with respect to ES cell technology in species other than mouse.

The art at the time of filing also held that the phenotype of gene knockout animals is unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These

knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

The guidance offered in the specification is limited to the production of gene-targeted mice using mouse ES cells (pages 22-23) resulting in a gene-targeted deletion of the mouse CCR8 gene. The specification does not disclose that ES cells from any species other than mouse can contribute to the germ line and therefore does not provide the necessary guidance for one of skill in the art to generate any species of transgenic animal lacking the CCR8 gene. Furthermore, the specification teaches the only phenotype of the claimed mouse wherein the mouse exhibits an altered Th2 immune response to allergen treatment (pages 23-25 and pages 29-32).

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the unpredictability of phenotype of animals lacking a CCR8 gene, the breadth of the claims with respect to all species of animals and the phenotype of the claimed animals, and the undeveloped state of the art with the availability of totipotent ES cells from species other than mouse, it would have required undue experimentation for one skilled in the art to make and use the claimed invention with a reasonable expectation of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (A) (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Capecchi (A) (Trends in Genetics, 1989, Vol. 5, pages 70-76) and further in view of Zingoni et. al. (Journal of Immunology, 1998, Vol. 161, pages 547-551 and Genbank accession number AF001277).

Claim 12 is drawn to a genetically engineered non-human animal whose genome lacks a CCR8 gene as a result of gene-targeted replacement of the CCR8 gene. Claim 13 limits the animal to rodent species. Claim 14 limits the animal to mouse. Claim 15 is directed to a genetically engineered non-human animal whose somatic and germ cells lack a CCR8 gene.

Capecchi (A) taught transforming a cell with a targeting construct comprising a disruption in the HoxA-3 gene (page 38, col. 3, paragraph 3), introducing the cell into a blastocyst (page 39, column 3, paragraph 2; page 38, Figure part 1), implanting the blastocyst into a pseudopregnant mouse (page 38, Figure part 2) and identifying a transgenic mouse comprising a disruption in the HoxA-3 gene (page 40, paragraph bridging columns 2 and 3). Capecchi differs from the claimed invention in that the targeting construct does target the CCR8 gene and, although inherent in the technique, Capecchi (A) does not explicitly teach disruption by gene replacement as opposed to disruptive insertion.

However, at the time the invention was made, Capecchi (B) taught that gene targeting vectors can be used to insert into or to replace endogenous genomic sequences (page 70, col. 2,

last full paragraph; page 72, col. 2, paragraphs 3-5) in mouse ES cells and the ES cells can be used to generate transgenic animals by the same methods taught by Capecchi (A). Capecchi (B) did not teach targeted replacement of the CCR8 gene.

However, at the time the claimed invention was made, Zingoni taught the cloning of the mouse CCR8 gene (page 547, col. 2, last para.).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to a knockout mouse having a replacement of a targeted gene as taught by Capecchi (A and B) wherein the gene was the CCR8 gene as taught by Zingoni. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene of Capecchi (A) or the *hprt* gene of Capecchi (B) with the CCR8 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the CCR8 gene to study the role of the allergic response of Th2 cells (page 547, col. 2, lines 16-18 and 23-25; page 551, col. 1, lines 5-7).

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Patent Examiner